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Real-world benefits of allergen immunotherapy for birch pollen-associated allergic rhinitis and asthma

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Abstract

Background: Real-world evidence is sparse on the benefits of allergen immunotherapy [AIT; subcutaneous/sublingual immunotherapy (SCIT/SLIT)], the only disease-modifying intervention for allergic rhinitis (AR) with long-term efficacy. This real-life study evaluated the effect of six AITs (native pollen SLIT/SCIT, four allergoid SCITs) vs symptomatic medication use, on AR symptoms and asthma symptoms/onset, in patients with birch pollen-associated AR and/or asthma.

Methods: In this retrospective cohort analysis of a German longitudinal prescription database, AIT patients received ≥2 successive seasonal treatment cycles; non-AIT patients had ≥3 AR prescriptions in three seasons or previous month. Patients were matched for: index year, age, gender, main indication at index, number of seasonal cycles within treatment period, baseline AR/asthma treatment prescriptions. Multiple regression analysis compared prescription data in AIT and non-AIT groups as proxy for clinical status/disease progression.

Results: Up to 6 years of follow-up, significantly more AIT (65.4%) vs non-AIT (47.4%) patients were AR medication-free; odds ratio (OR) [95% confidence interval (CI)]: 0.51 [(0.48-0.54); $P < 0.001$] (28.6% covariate-adjusted reduction vs non-AIT; $P < 0.001$), and significantly more AIT (49.1%) vs non-AIT (35.1%) patients were asthma medication-free [OR (95% CI): 0.59 (0.55-0.65); $P < 0.001$] (32% reduction vs non-AIT; $P < 0.001$), or reduced existing asthma medication use (32% covariate-adjusted reduction vs non-AIT; $P < 0.001$). During treatment, new-onset asthma risk was significantly reduced in the AIT vs non-AIT group (OR: 0.83; $P = 0.001$).

Conclusions: Birch pollen AIT demonstrated real-world benefits up to 6 years post-treatment cessation through significantly reduced AR and asthma medication intake, and significantly decreased risk of new-onset asthma medication use on-treatment.

KEYWORDS

allergic rhinitis, asthma, real-world evidence, subcutaneous immunotherapy, sublingual immunotherapy

1 | INTRODUCTION

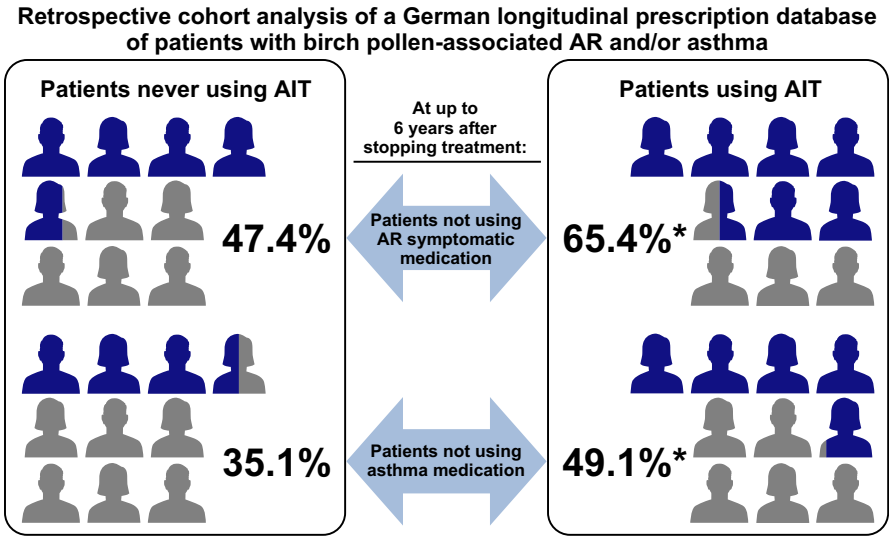
Allergic rhinitis (AR) is a common inflammatory condition associated with bothersome symptoms affecting the upper airways, nose and eyes.[1,2] AR affects up to 40% of the population worldwide, including 23%-30% of people within Europe.[3] Birch pollen is among the top three most-diagnosed allergens responsible for respiratory allergies,[4] and birch is considered to be the major pollen-allergen-producing tree in northern Europe,[5] inducing mostly nasal symptoms.[6] AR represents a considerable burden on public health, impacting daily activities, quality of life and productivity.[1] It is also frequently associated with various comorbidities, including asthma.[1,7-10] AR often precedes asthma,[11-13] with the progression from AR to asthma considered part of the "allergic march",[14] while uncontrolled AR may be associated with worsening of coexisting asthma.[15]

Allergen immunotherapy (AIT), in the form of subcutaneous or sublingual immunotherapy (SCIT/SLIT), is the only treatment for AR and/or allergic asthma (AA) with long-term efficacy.[16-19] In randomized, double-blind, placebo-controlled studies, precoseasonal administration of birch pollen SLIT for 2 years led to a significant and sustained reduction in symptoms and symptomatic medication use in patients with birch pollen-associated allergic rhinoconjunctivitis (ARC)[5] and patients with AR plus asthma.[20] However, long-term data from the real-world setting, assessing the preventative role of different AIT preparations on AR and/or AA progression, are sparse.[5,20-24] Real-world studies are particularly valuable because they can allow for longer observation periods and larger, more heterogeneous patient cohorts than clinical trials.

There is ongoing debate on which, if any, is more effective in AIT: native or modified allergen extracts, and SCIT or SLIT. It was recently suggested that native preparations might be more effective[25]; on the other hand, modified preparations are usually associated with a lower side-effect rate.[26,27]

Therefore, in the present analysis, we compared in a real-life situation the effectiveness of 6 different birch or three-tree (birch, alder, hazel) pollen AITs (native SLIT/SCIT and 4 allergoid SCIT preparations) vs a non-AIT control group receiving symptomatic treatment only, in patients with birch family pollen-associated AR and/or AA, to assess: (1) impact on AR progression, measured with use of symptomatic AR medication ± AIT after active treatment cessation; (2) impact on asthma occurrence in nonasthmatic patients, during treatment and after active treatment cessation and (3) impact on asthma progression in asthmatic patients, measured by the use of symptomatic asthma medication ± AIT after active treatment cessation.

This is the third analysis involving the LRx database and follows two previous publications that demonstrated the long-term, real-world benefits of grass pollen SLIT in patients with AR with or without associated asthma in terms of slower AR progression, reduced risk of new AA onset in AR patients with no associated asthma comorbidity and slower AA progression in the AR population with concomitant asthma.[21,24]



*p<0.001 versus patients not using AIT
AIT, allergen immunotherapy (either native pollen SLIT drops, native pollen SCIT, or 4 allergoid SCITs);
AR, allergic rhinitis; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy

GRAPHICAL ABSTRACT

In this retrospective, real-world study in Germany, birch pollen allergen immunotherapy (AIT) demonstrated significant benefits up to 6 years post-treatment in patients with birch pollen-associated allergic rhinitis (AR) and/or asthma. AIT was associated with significantly improved AR and asthma symptoms as the medication dispensing decreased; nearly two-thirds and one-half of patients initially using AR or asthma medications, respectively, no longer required them at study end. During the period in which they were receiving AIT, patients with AR but not asthma had a significantly decreased risk of new-onset asthma medication dispensing.

2 | METHODS

2.1 | Overall study design

This was a retrospective analysis of data extracted from a German longitudinal prescription database (LRx, IQVIA, Frankfurt am Main, Germany). The overall analysis period was June 2009 to February 2017.

Six birch family pollen AIT products available in Germany and indicated for both AR and mild-to-moderate AA treatment were analysed: natural SLIT drops, natural SCIT and four allergoid SCIT preparations [two birch pollen extract formulations (Allergoid SCIT 1 and 2), a depigmented, polymerized birch pollen extract formulation (Allergoid SCIT 3) and a formulation designed for ultra-short-course administration (Allergoid SCIT 4)]. These products were chosen based on the "List of AIT products in Germany" provided by the German Society for Allergology and Clinical Immunology, in the context of the current guideline on AIT in IgE-mediated allergic diseases,[28] and were either "authorized allergen preparations with documented efficacy and safety, or preparations tradeable under the German Therapy Allergen Ordinance, for which efficacy and safety have already been documented in clinical trials meeting World Allergy Organization".[29,30]

2.2 | Datasets and proxy clinical data

The LRx database is updated monthly and contains information on ~60% of all prescriptions claimed by patients and reimbursed by statutory health insurance funds in Germany. The dispensing date, prescribing physician's Speciality, and full details of the medication (brand, formulation, active compound, dose level, etc.) are provided for each prescription. Patients' age and gender are known in most cases, and in line with German legislation on anonymized database analysis, informed consent is not required. The LRx database does not contain clinical information (eg, diagnoses); hence, patient profiles (eg, presence and/or progression of birch pollen AR and/or asthma) must be inferred from proxy prescription data.

2.3 | Analytical time periods

For the AIT group, index date was defined as date of first prescription of one of the selected AIT products. For the control group, index date was defined as date of the second of three relevant prescriptions in three consecutive three-tree pollen seasons. This had to be in the same index seasonal cycle as the index date of the individual product patient matched to the corresponding control patient.

The pre-index period was defined as the 365 days before index date, and the treatment period was from index date of the first AIT product to expiry date of the last prescription of this product. The follow-up period was from end of the treatment period to end of study, and the full-analysis period combined the treatment and follow-up periods.

2.4 | Patients and inclusion/exclusion criteria

Patients meeting the following criteria were included in the overall AIT group: age ≥5 years; received treatment in ≥2 successive three-tree pollen seasonal cycles with one of the selected AIT products; initiated treatment with one of these products between June 2009 and May 2013; had ≥1 defining prescription against AR (nasal corticosteroids, oral/systemic antihistamines) in the 365 days before index date and/or ≥2 defining prescriptions against asthma [inhaled corticosteroids (ICS), ICS/long-acting beta agonists, short-acting beta agonists] in the three-tree pollen seasonal cycle defined by index season or the one immediately preceding it; and ≥2 years of follow-up (ie, observability) after treatment end.

Patients were excluded if they had received one of the selected AIT products in the three-tree pollen seasonal cycle before index date; had received >1 of the selected products in their entire database history (the only exception was switching between birch and three-tree pollen formulations inside one of the individual product groups); had received any other AIT product in their entire database history; had severe asthma (defined as having prescriptions of biologics for asthma); or had perennial asthma [defined as ≥3 prescriptions of ICS or methylxanthines, distributed over three successive 4-month periods (one such prescription each in January to April, May to August and September to December) before or over the pollen seasonal cycle of the index date] without exacerbations during the season.

The control group included patients with AR and/or asthma due to birch or three-tree pollen who had not received any AIT treatment in their entire database history. Patients in the control group underwent exact matching with those in the AIT group using the following criteria: index year, number of seasonal cycles covered by the treatment period, age group at index date (5-17, 18-35, 36-50 and >50 years), closest age match inside age group, gender (male/female/unknown), main indication status at index date (AR, asthma or both) and number of prescriptions of AR/asthma treatment in the pre-index period. To ensure that all medications were actually prescribed for birch/three-tree pollen allergy, it was also required that at least the identifying prescriptions were dispensed during the three-tree pollen season (February to May) or the month before it (January).

2.5 | Study endpoints

Study endpoints and primary analyses included: (1) AR progression from 2 to 6 years after active treatment cessation in patients with AR (± asthma) at baseline; (2) occurrence and time to development of asthma in patients with AR without associated asthma at baseline, during treatment and from 2 to 6 years post-treatment; and (3) asthma progression from 2 to 6 years after active treatment cessation in patients with asthma (± AR) at baseline. Secondary analyses duplicated the primary analyses, but with the AIT group split into 6 individual AIT product subgroups, and the non-AIT control group acting as the reference for comparisons.

2.6 | Statistical analysis

Descriptive statistics were presented for all outcome variables and covariates, split by grouped or individual products (ie, overall AIT, non-AIT control, natural SLIT, natural SCIT and four individual allergoid SCIT formulations). Analyses of medication intake progression (AR or asthma) were carried out by regression using a general linear model, with the ratio of annual number of prescriptions in the analysis period vs the pre-index period used as the outcome variable. Analysis of asthma medication intake as a Y/N variable was achieved by logistic regression. Because the probability of asthma medication intake occurrence would also depend on length of analytical time span, the individual length of this period was included as a covariate. Time to asthma medication intake was investigated using survival analysis. The proportion of patients with any level of treatment between the AIT and non-AIT control groups was also analysed by logistic regression. Statistical analyses were based on two-way testing without exception. For all statistical tests, significance level was set to 5% ($P < 0.05$). Analyses were performed using SAS 9.4 software SAS Institute, Inc., Cary, NC, USA.

3 | RESULTS

In total, 9001 AIT patients and 45 005 matched non-AIT control patients were included, and their demographic and prescription-related characteristics at index are shown in Table 1. The majority of patients (~85% for both AIT and non-AIT groups) underwent ≤3 seasonal cycles of treatment (Table 2), and only 14.8% of AIT patients were treated for longer. The follow-up period was slightly longer for

TABLE 1 Demographic and prescription-related characteristics of patients in the AIT (overall and by product) and non-AIT groups at index date or during the pre-index period

Parameter, n (%)	Non-AIT control	All AIT	Natural SLIT	Natural SCIT	Allergoid SCIT 1	Allergoid SCIT 2	Allergoid SCIT 3	Allergoid SCIT 4
Patient disposition								
Available for matching	433 140 (100.0)	14 018 (100.0)	1282 (100.0)	1555 (100.0)	5714 (100.0)	2514 (100.0)	1464 (100.0)	1489 (100.0)
Successfully matched	45 005 (10.4)	9001 (64.2)	838 (65.4)	1020 (65.6)	3728 (65.2)	1600 (63.6)	881 (60.2)	934 (62.7)
Using AR treatment before index	31 745 (7.3)	6349 (45.3)	634 (49.5)	755 (48.6)	2603 (45.6)	1120 (44.6)	630 (43.0)	607 (40.8)
Using asthma treatment before index	10 900 (2.5)	2180 (15.6)	170 (13.3)	221 (14.2)	919 (16.1)	392 (15.6)	210 (14.3)	268 (18.0)
Using both AR and asthma treatments before index	2360 (0.5)	472 (3.4)	34 (2.7)	44 (2.8)	206 (3.6)	88 (3.5)	41 (2.8)	59 (4.0)
Age distribution at index, years								
5-17	8960 (19.9)	1792 (19.9)	193 (23.0)	199 (19.5)	667 (17.9)	320 (20.0)	253 (28.7)	160 (17.1)
18-35	9700 (21.6)	1940 (21.6)	161 (19.2)	214 (21.0)	849 (22.8)	325 (20.3)	193 (21.9)	198 (21.2)
36-50	15 410 (34.2)	3082 (34.2)	258 (30.8)	365 (35.8)	1298 (34.8)	564 (35.3)	267 (30.3)	330 (35.3)
>50	10 935 (24.3)	2187 (24.3)	226 (27.0)	242 (23.7)	914 (24.5)	391 (24.4)	168 (19.1)	246 (26.3)
Gender distribution at index								
Male	13 640 (30.3)	2728 (30.3)	274 (32.7)	283 (27.7)	1137 (30.5)	477 (29.8)	263 (29.9)	294 (31.5)
Female	17 760 (39.5)	3552 (39.5)	320 (38.2)	389 (38.1)	1498 (40.2)	661 (41.3)	327 (37.1)	357 (38.2)
Unknown	13 605 (30.2)	2721 (30.2)	244 (29.1)	348 (34.1)	1093 (29.3)	462 (28.9)	291 (33.0)	283 (30.3)
Prescribing physician								
ENT specialist	6232 (13.8)	2709 (30.1)	273 (32.6)	369 (36.2)	1200 (32.2)	401 (25.1)	237 (26.9)	229 (24.5)
Dermatologist	1945 (4.3)	2426 (27.0)	169 (20.2)	356 (34.9)	892 (23.9)	570 (35.6)	270 (30.6)	169 (18.1)
Pneumologist	1952 (4.3)	1335 (14.8)	70 (8.4)	53 (5.2)	730 (19.6)	233 (14.6)	92 (10.4)	157 (16.8)
Paediatrician	4461 (9.9)	936 (10.4)	62 (7.4)	85 (8.3)	307 (8.2)	178 (11.1)	185 (21.0)	119 (12.7)
Internal specialist	6534 (14.5)	417 (4.6)	36 (4.3)	47 (4.6)	183 (4.9)	60 (3.8)	26 (3.0)	65 (7.0)
General practitioner	23 394 (52.0)	1109 (12.3)	208 (24.8)	99 (9.7)	399 (10.7)	151 (9.4)	66 (7.5)	186 (19.9)
Other speciality	487 (1.1)	69 (0.8)	20 (2.4)	11 (1.1)	17 (0.5)	7 (0.4)	5 (0.6)	9 (1.0)

AIT, allergen immunotherapy; AR, allergic rhinitis; ENT, ear, nose and throat; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

TABLE 2 Pattern of treatment administration in the patient groups receiving AIT

Parameter, n (%)	Non-AIT control (N = 45 005)	All AIT (N = 9001)	Natural SLIT (N = 838)	Natural SCIT (N = 1020)	Allergoid SCIT 1 (N = 3728)	Allergoid SCIT 2 (N = 1600)	Allergoid SCIT 3 (N = 881)	Allergoid SCIT 4 (N = 934)
Seasonal cycles in treatment period								
2	20 290 (45.1)	4058 (45.1)	328 (39.1)	399 (39.1)	1702 (45.7)	691 (43.2)	485 (55.1)	453 (48.5)
3	18 070 (40.2)	3614 (40.2)	307 (36.6)	418 (41.0)	1522 (40.8)	643 (40.2)	301 (34.2)	423 (45.3)
4	5985 (13.3)	1197 (13.3)	183 (21.8)	183 (17.9)	451 (12.1)	242 (15.1)	89 (10.1)	49 (5.2)
5	660 (1.5)	132 (1.5)	20 (2.4)	20 (2.0)	53 (1.4)	24 (1.5)	6 (0.7)	9 (1.0)
Average (SD)	2.71 (0.75)	2.71 (0.75)	2.88 (0.83)	2.83 (0.79)	2.69 (0.74)	2.75 (0.76)	2.56 (0.70)	2.59 (0.64)
Duration of follow-up period, years								
Average (SD)	4.16 (1.09)	4.41 (1.06)	4.35 (1.01)	4.61 (0.99)	4.52 (1.06)	4.38 (1.07)	3.97 (0.96)	4.31 (1.11)
Range	1.75-6.08	2.00-6.61	2.00-6.48	2.01-6.56	2.01-6.61	2.01-6.52	2.01-5.56	2.00-6.43

AIT, allergen immunotherapy; SCIT, subcutaneous immunotherapy; SD, standard deviation; SLIT, sublingual immunotherapy.

the AIT vs non-AIT group (Table 2), mainly due to differing treatment patterns: symptomatic treatment is given during the pollen season, whereas AIT should start before the pollen season commences.

3.1 | Progression of AR medication intake after treatment cessation

At up to 6 years of follow-up, significantly more patients in the AIT group (n = 4459 of 6821 patients with AR at baseline; 65.4%) vs non-AIT group (n = 16 152 of 34 105 patients with AR at baseline; 47.4%) were treatment-free [odds ratio (OR) [95% confidence interval (CI)] for AIT: 0.51 (0.48-0.54), $P < 0.001$] (Figure 1A), equating to a 28.6% greater reduction in prescriptions in the AIT group after covariate adjustment than the non-AIT group ($P < 0.001$) (Figure 1B).

At follow-up, a greater reduction from baseline was noted in all AIT groups for average number of AR medication prescriptions per patient per year [(baseline vs follow-up values): overall AIT and allergoid SCIT 1, both 1.72 vs 0.25; allergoid SCIT 2, 1.71 vs 0.23; allergoid SCIT 3, 1.68 vs 0.28; allergoid SCIT 4, 1.75 vs 0.31; natural SCIT, 1.72 vs 0.22; natural SLIT, 1.73 vs 0.23], compared with the non-AIT group (baseline: 1.73 vs follow-up: 0.70).

3.2 | New asthma medication onset

Of 9001 AIT and 45 005 non-AIT patients, 6349 (70.5%) and 31 683 (70.4%), respectively, did not have asthma at baseline. Of these, 793 (12.5%) AIT and 4159 (13.1%) non-AIT patients subsequently developed asthma (Figure 2).

During treatment, AIT patients had a significantly reduced risk of new-onset of asthma medication intake vs non-AIT patients (OR: 0.83; $P = 0.001$) (Figure 3A). Up to 6 years after stopping treatment, none of the products prevented the occurrence of new-onset of asthma medication intake in nonasthmatic patients. During the follow-up/post-treatment period, the OR for the AIT group was close to equality and therefore not significant (OR: 1.02, $P = 0.77$) (Figure 3B). Over the 8-year full-analysis period, there was no significant reduction in risk of new-onset AA in the AIT vs non-AIT group (OR: 0.94; $P = 0.16$) (Figure 3C).

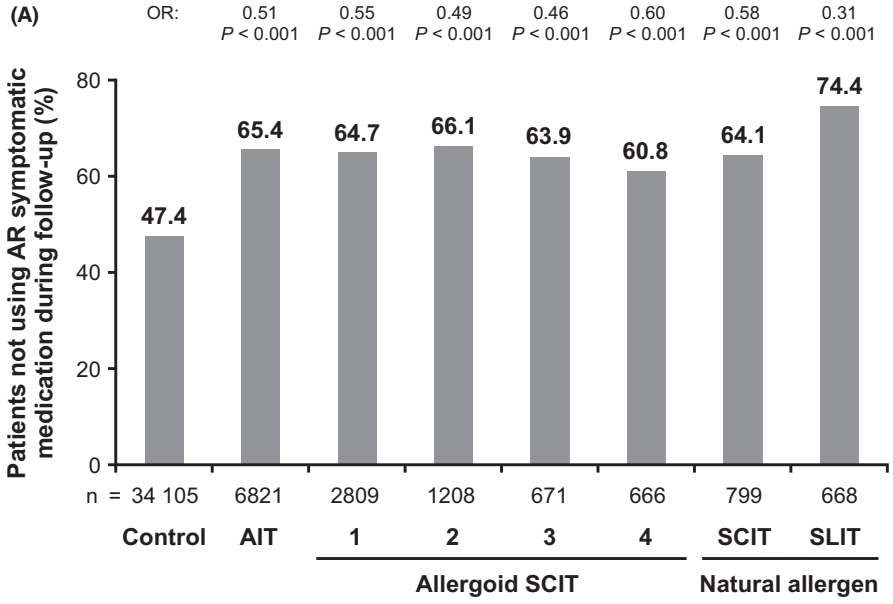
3.3 | Progression of asthma medication after treatment cessation

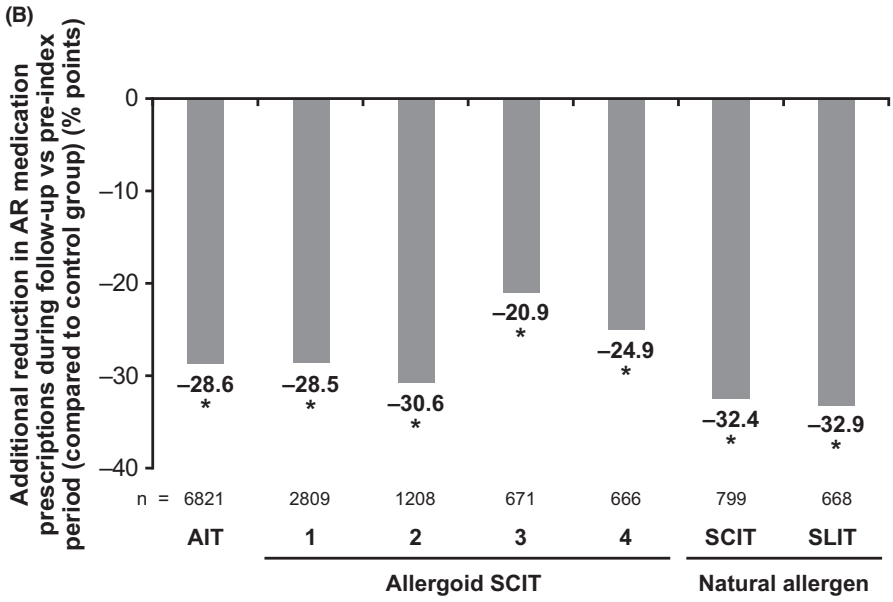
At up to 6 years of follow-up, significantly more patients in the AIT group (n = 1302 of 2652 using asthma therapy at baseline; 49.1%) vs non-AIT group (n = 4654 of 13 260 using asthma therapy at baseline; 35.1%) were asthma medication-free [OR (95% CI) for AIT: 0.60 (0.55-0.65); $P < 0.001$] (Figure 4A). In the follow-up/post-treatment period, significantly less asthma medication was used in the AIT vs non-AIT group after covariate adjustment (32% reduction vs non-AIT; $P < 0.001$) (Figure 4B).

At follow-up, a greater reduction from baseline was noted in all AIT groups for average number of asthma medication prescriptions per patient per year [(baseline vs follow-up values): overall AIT (2.10 vs 0.61), allergoid SCIT 1 (2.07 vs 0.60), allergoid SCIT 2 (2.05 vs 0.65), allergoid SCIT 3 (2.14 vs 0.58), allergoid SCIT 4 (2.09 vs 0.72), natural SCIT (2.14 vs 0.58), natural SLIT (2.23 vs 0.49)], compared with the non-AIT group (baseline: 2.11 vs follow-up: 1.28).

4 | DISCUSSION

This retrospective, longitudinal analysis of the German LRx database demonstrated that birch family pollen AIT was associated with significantly reduced AR progression, ie, less need for symptomatic medication. Nearly half of non-AIT and two-thirds of AIT patients were no longer prescribed symptomatic AR treatment during the follow-up period. In the AIT group, this may be largely or even entirely due to the effect of AIT to attenuate disease severity; in both groups, particularly the non-AIT group, this may be partly associated with natural development of tolerance to the allergen. The level of baseline AR treatment was higher in the non-AIT group and was subsequently artificially reduced by matching to AIT patients. Therefore,





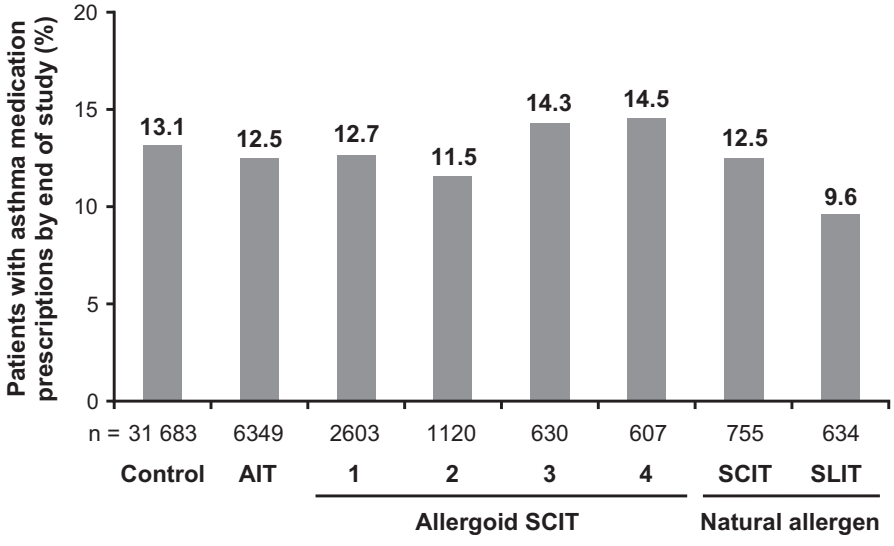


FIGURE 1 Proportion of patients not using AR symptomatic medication (A) and percentage-point reduction from baseline in AR symptomatic medication prescriptions (B) during follow-up. *$P < 0.001$ vs non-AIT control group. AIT, allergen immunotherapy; AR, allergic rhinitis; OR, odds ratio; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy

FIGURE 2 Proportion of patients with birch family pollen-associated AR but no concomitant asthma at baseline who started asthma medication use by end of study. AIT, allergen immunotherapy; AR, allergic rhinitis; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy

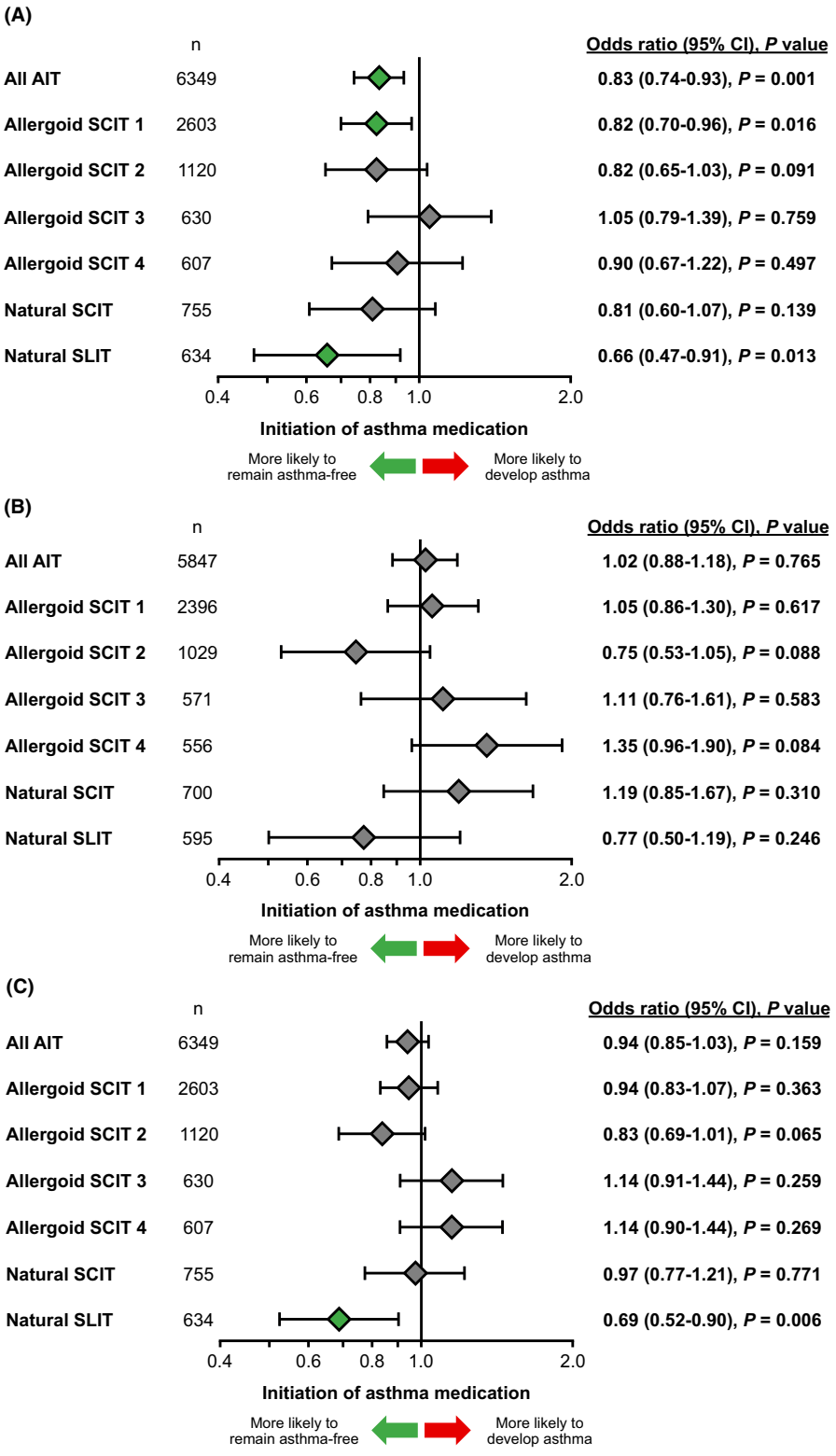


FIGURE 3 Odds of starting asthma medication use during the treatment (A), post-treatment (B) or full-analysis (C) periods in patients with birch family pollen-associated AR but no concomitant asthma at baseline. AIT, allergen immunotherapy; CI, confidence interval; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy

the proportion of patients able to stop symptomatic AR treatment may have been artificially increased in this group, meaning that the comparative effectiveness of AIT on AR symptoms may be even greater than that observed in the study.

This study also showed a significant reduction in the progression of asthma medication use and a significantly decreased risk of new-onset asthma medication use during treatment with AIT. Analysis of asthma medication occurrence showed that AIT might be associated with a significantly reduced risk of developing asthma during treatment, but a persistent post-treatment effect could not be shown. Statistical power to detect an effect on new-onset asthma may have been lowered, due to relatively few patients developing asthma and

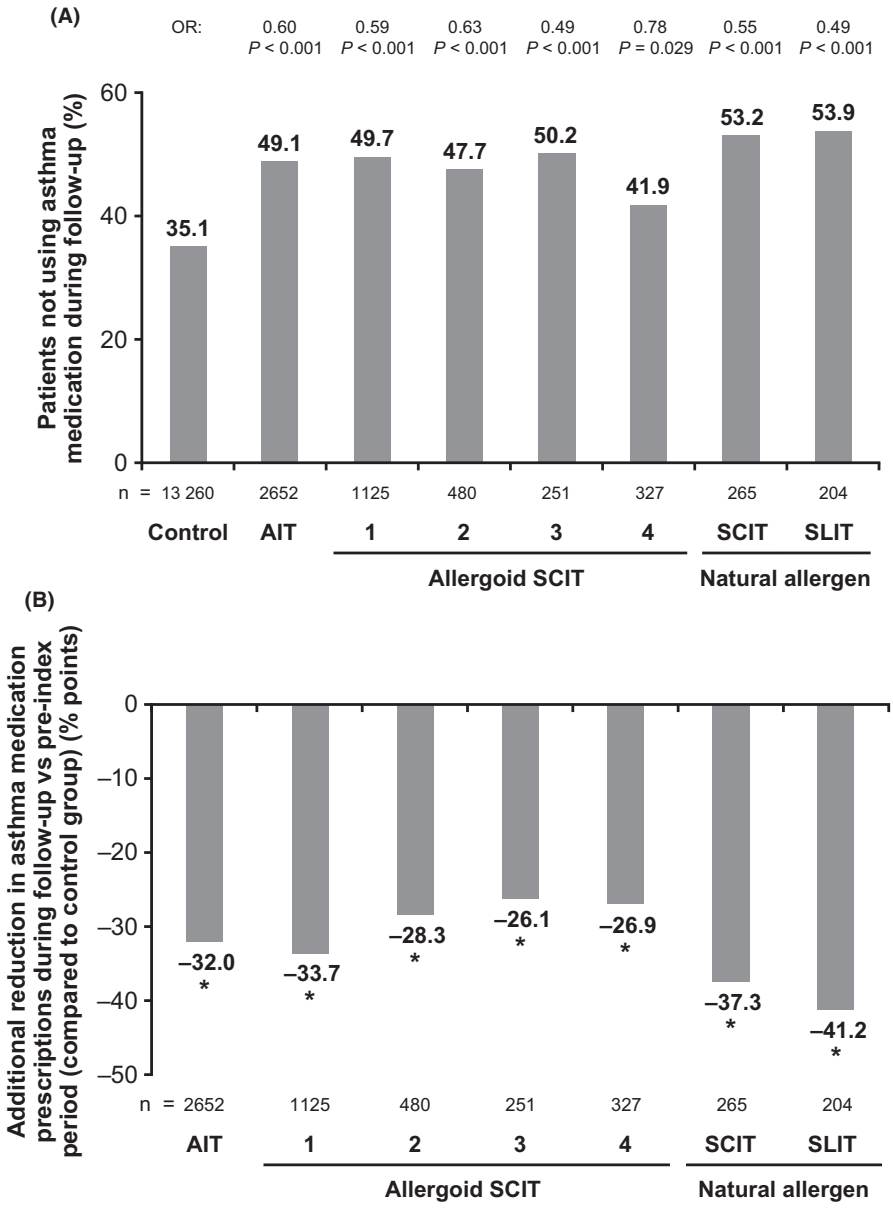


FIGURE 4 Proportion of patients not using asthma medication (A) and percentage-point reduction from baseline in asthma medication use (B) during follow-up. *$P < 0.001$ vs non-AIT control group. AIT, allergen immunotherapy; OR, odds ratio; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy

the low proportion of patients aged <18 years in the study (the ability of AIT to prevent asthma appears to be greatest in children[29]). These findings are in contrast to those in a previous grass pollen SLIT study,[21] in which a sustained beneficial effect of SLIT on lowering new-onset asthma risk was noted in the post-treatment period. However, the grass pollen SLIT study included a much higher proportion of children in the AIT group than did the present study (~50% vs ~20%, respectively).

The present real-world findings add to the current body of clinical evidence demonstrating the benefits of AIT in patients with birch pollen-associated AR. In a randomized, double-blind, placebo-controlled Phase IIIb study in patients with birch-associated ARC (N = 574), treatment for two consecutive pre- and coseasonal periods with birch pollen SLIT was associated with a sustained reduction in symptoms and medication use, measured with the Average Adjusted Symptom Score.[5] In a randomized, double-blind, placebo-controlled study of birch pollen SLIT administered using a precoseasonal protocol repeated for 2 years in patients presenting with severe rhinitis and slight to moderate asthma (N = 24), median number of days with asthma at visit 3 was 10 vs 13 in the SLIT and placebo groups, respectively, and at visit 6 was 2 vs 7, respectively ($P < 0.05$ between groups). A reduction in asthma medication intake occurred in 77% of actively treated vs 0% of placebo-treated patients ($P = 0.05$).[20]

Allergoids are derived by chemical modification of allergens using formaldehyde or glutaraldehyde (often followed by adsorption to a carrier, such as aluminium hydroxide, tyrosine or monophosphoryl lipid A). This modification process induces conformational changes in allergen proteins, so that they possess less-reactive B-cell epitopes and thus reduced IgE binding, while their T-cell epitopes and immunogenic effect remain unaltered. In comparison to native allergens, a less-pronounced allergic reaction occurs with

allergoids because IgE-binding sites are rendered inactive by their altered chemical structure and fewer IgE antibodies can bind. Allergoids therefore exhibit lower allergenicity at the same level of immunogenicity as native allergens[19] and can be administered at higher doses than native preparations. In the present study, the effectiveness of the native SLIT or SCIT formulations was not inferior to that of the allergoid formulations. Therefore, dosing regimens and adherence may be additional considerations for the patient and physician when choosing to use AIT. Over 3 years, SLIT is administered daily pre- and coseasonally, conventional SCIT comprises >40 injections and ultra-short-course formulations require just four injections; as shown in the present study, the latter are effective but may have a more modest magnitude of improvement compared with formulations that follow conventional or short-course administration.

Allergen immunotherapy also has significant benefits in reducing asthma risk in patients with grass pollen-associated AR, ARC and/or asthma. In the SQ grass SLIT tablet asthma prevention (GAP) study in children aged 5-12 years with grass pollen-associated AR (and no asthma) at enrolment (N = 812), 3 years of SLIT treatment significantly reduced the risk of experiencing asthma symptoms or using asthma medication after a 2-year, untreated follow-up period and over the 5 years of the study (OR: 0.66; $P < 0.036$). Moreover, both ARC symptoms and symptomatic medication use were significantly reduced, by 22%-30% ($P < 0.005$ for all 5 years) and 27% vs placebo ($P < 0.001$), respectively.[23] Similarly, the Preventive Allergy Treatment (PAT) study showed that a 3-year course of SCIT with standardized allergen extracts (birch and grass pollen) in children resulted in long-term clinical effects, with a significantly lower asthma incidence among SCIT-treated patients (relative to symptomatic medication alone) observed at 7 years after treatment cessation.[22,31] Finally, the prior analyses of the LRx database provide real-world evidence of the long-term benefits of grass pollen SLIT in patients with AR with or without associated asthma in terms of slower progression of AR and AA medication intake, and reduced risk of new-onset asthma medication use.[21,24]

The current study used an improved patient-matching process, compared with the aforementioned grass pollen SLIT LRx database analysis.[21,24] Patients were stratified into AIT or non-AIT groups and matched by index year, age group, gender, main indication (AR/AA) at index date, number of seasonal cycles while on treatment and baseline AR/AA treatment prescriptions. This reduced confounding and wide differences in covariate distribution helped align groups by treatment-period duration and avoided possible bias from intergroup differences in baseline treatment levels. All AIT patients satisfying inclusion/exclusion criteria were analysed and then matched 1:5 with non-AIT patients; therefore, the covariate distributions observed reflect those of the overall AIT group, but may differ significantly from those of the general non-AIT patient population before matching.

The high proportion of patients with unknown gender reflects German practice in not recording gender information on prescriptions. Instead, this was deduced/inferred from the first name of the patient, and in cases of ambiguity, patients were recorded as having "unknown" gender. Nevertheless, where known, the gender distribution was consistently and notably skewed towards female in the AIT group. It is unclear whether this reflects a genuine clinically relevant, increased sensitivity of females to birch family pollen or just an artefact of the selection process, because a study conducted in children and adolescents in Germany reported a higher sensitization to birch pollen among boys than girls.[32]

Differences in prescriber speciality between AIT and non-AIT groups reflect prescribing practice in Germany: AIT is mainly administered by ear, nose and throat (ENT) specialists and dermatologists, while symptomatic treatment is typically prescribed by ENT specialists (if AR) or pneumologists (if asthma). Moreover, most of the analysed AIT products (excluding SLIT) must be administered by a physician, unlike symptomatic medication, meaning that the general practitioner plays a large role in treatment of the non-AIT group, compared with the AIT group.

This study had several limitations. No diagnoses are recorded in the LRx database, meaning AR and asthma medication use had to serve as a proxy to identify disease. Notably, there may have been a risk of "false-negatives" (ie, patients suffering from disease but not identified) among patients with AR, because a large proportion of AR medication (particularly antihistamines) is available over-the-counter (OTC). This can affect both patient selection and subsequent assessment of AR progression. Nevertheless, any such bias should have impacted both AIT and non-AIT groups equally, meaning that the relative between-group comparisons and conclusions remain valid. It was not possible to capture OTC medication use in the study; however, in a survey of patients in France, Germany and the UK with asthma and diagnosed AR (N = 936), 50% self-reported that they received AR medication prescriptions, while 21% used OTC AR medications.[33] The height of the birch pollen season in Germany is April to early May, but it was assumed to extend further into May for the present study; therefore, patients selected via medication use in that month may have suffered from grass pollen- instead of birch pollen-associated AR, particularly those in the non-AIT group who did not have confirmation of a prescription for birch pollen-specific AIT. While study inclusion/exclusion criteria were designed to rule out polyallergy leading to AIT use against more than one pollen type (or other allergens such as house dust mites), this may not have been possible to completely achieve in practice. Finally, it was not possible to check patient observability directly because the LRx database only collects data on reimbursed prescriptions; however, the necessity to have ≥1 AR and/or asthma prescription(s) in the year before index acted partly as a proxy for checking observability, and in fact eliminated around two-thirds of patients using AIT.

The main strengths of this study are that it was conducted in a real-world, large and inclusive patient cohort, with long-term follow-up. It demonstrated high external validity (the study mirrors current German clinical practice), and the stringent patient matching ensured robustness of findings.

5 | CONCLUSIONS

This real-world study demonstrates the long-term benefits of birch family pollen AIT up to 6 years after treatment cessation via a significantly reduced progression of AR and asthma medication intake, and a significantly decreased risk of new-onset asthma medication use during treatment.

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CONFLICT OF INTEREST

U Wahn has received consulting fees from Allergopharma, Danone, Hipp, Merck, Novartis, IMS Health GmbH & Co and Stallergenes Greer; honoraria for lectures from ALK-Abelló, Allergopharma, Allergy Therapeutics, LETI, MSD, Nestlé, Novartis, Nutricia and Stallergenes Greer; and research funding from Stallergenes Greer. C Bachert has received consulting fees or honoraria for lectures from ALK-Abelló, Stallergenes Greer, HAL Allergy and IMS Health GmbH & Co. S Zielen has received fees for lectures and advisory boards from ALK-Abelló Arzneimittel GmbH, Allergopharma GmbH, Allergy Therapeutics, Lofarma GmbH, bene-Arzneimittel GmbH, Biotest, Boehringer Ingelheim, GlaxoSmithKline GmbH, IMS Health GmbH & Co. OHG, Novartis AG and Vifor Pharma Deutschland GmbH. J Heinrich has received consulting fees from Boehringer Ingelheim, IMS Health GmbH & Co. OHG and Kabi. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

AUTHOR CONTRIBUTIONS

All authors contributed to the design and implementation of the research, the analysis of the results and the development of the manuscript, and approved its submission.

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